REMARKS

Claims 18, 20, 21, 23, 31, 33, 36, 51 and 52 are pending in the present Application. Claim 23 has been amended as suggested by the Examiner to eliminate the term "high." No claims have been added or canceled. Reconsideration and allowance of claims 18, 20, 21, 23, 31, 33, 36, 51 and 52 are respectfully requested in view of the above amendments and the following remarks.

Oath/Declaration

The Applicants thank the Examiner for pointing out the typographical error in the priority claim, and submit herewith a supplemental application data sheet correcting the provisional application serial number.

Specification

The Specification has been amended to correct the filing date for the provisional application. No new matter has been introduced by these amendments.

As the filing date for the provisional application has been corrected, Applicant requests withdrawal of the objection to the specification.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 23 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner is concerned that the term “high” is not defined.

Applicants thank the Examiner for his suggested claim amendment to overcome this rejection and have amended claim 23 accordingly. Accordingly, Applicants submit that this ground for rejection has been obviated.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 31 and 36 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Hardy et al (Journal of Virology 77(3): 2029-2037, 2003) in view of Zhong et al (Antimicrobial Agents and Chemotherapy 47(8): 2674-2681, 2003) and Mueller et al (Journal of Biological Chemistry 261(25): 11756-11764, 1986). More specifically, the Examiner is of the view that Hardy teaches a method for determining whether a test compound is an RNA synthesis inhibitor

of a positive strand RNA virus using all of the steps recited in claim 31 except that the assay of Hardy (a) does not assess RNA synthesis initiation and (b) quantifies the final transcripts without using a RNase protection assay. The Examiner finds these elements in a combination of Zhong (which describes dinucleotide analogs as inhibitors of RNA synthesis initiation in hepatitis C virus) and Mueller's teaching of an RNase protection assay. The Examiner believes that is does not matter that Mueller's assay was performed in yeast because a person of skill in the art would understand that "general molecular biology techniques such as taught by Mueller were applicable across diverse fields of study" (Office Action dated January 13, 2010 at page 10).

Applicants respectfully traverse this rejection. Hardy teaches an *in vitro* replication system that can be used to identify inhibitors of RNA synthesis. Such inhibitors may be inhibitors of initiation, but may alternatively be inhibitors of elongation. There is no way to distinguish between the two using the assay of Hardy. In fact, the assay of Hardy was unable to detect *de novo* initiation at all (Hardy page 2033, left column). Accordingly, a person of ordinary skill in the art, wishing to identify inhibitors of initiation, would not choose to start with the assay of Hardy, which is known to be unable to detect such inhibitors. Hardy further does not teach or suggest targeting the initiation region to search for initiation inhibitors, and does not teach or suggest hybridizing a probe complementary to the initiation region of the newly synthesized RNA. Thus, Hardy does not provide an assay capable of detecting inhibitors of RNA synthesis initiation, or any motivation to target the initiation region of newly synthesized RNAs to test for viral RNA initiation inhibitors.

Zhong is relied upon for the teaching of dinucleotide analogs as inhibitors of RNA synthesis initiation in hepatitis C virus. Zhong's assay uses short RNA templates having the sequence 5' AAAAAAAAGC 3'. Complementary RNA synthesis by the RNA polymerase NS5B is then assayed using GTP and radiolabeled CTP, followed by detection of the radiolabeled pppGpC product (Zhong, Figure 2 and legend). Zhong then uses this assay to detect the effect of dinucleotide analogs on synthesis the product.

The Examiner views Zhong as supplying the motivation to use the assay of Hardy to identify inhibitors of RNA synthesis initiation, but Applicants respectfully disagree. First, the method used by Zhong differs substantially from the present invention; for example, detection is performed directly by electrophoresis of the labeled product, rather than using an RNase protection assay. Accordingly, Zhong does not teach or suggest hybridizing a probe

complementary to the initiation region of the newly synthesized RNA, as recited in claim 31. In addition, the polymerase used is recombinant, instead of being present within an isolated replication complex. It is unclear whether the inhibitors identified by Zhong would also inhibit initiation by the replication complex. Second, even if there is overlap in the activity of the inhibitors, Zhong fails to teach or suggest the possibility that the assay of Hardy could be modified to detect inhibitors of initiation. As noted above, the Hardy assay was described as being incapable of detecting such inhibitors. Nothing in Zhong addresses this point, or suggests that the Hardy assay might be a useful starting point for developing an assay for initiation inhibitors.

Mueller is relied upon for the teaching of RNAse protection assays. Mueller describes such an assay to detect relative rates of transcription of yeast mitochondrial genes *in vivo*, in intact yeast cells. That assay differs from the presently claimed assay in that the present organism is completely different and the present assay is performed in a cell-free system. It is a substantial leap to apply an assay that is known for use *in vivo* in yeast to a cell-free context, using viral RNA. A person of ordinary skill in the art of molecular biology would be aware that difficulties are commonly encountered when modifying an *in vivo* procedure so as to apply it in an *in vitro* setting, and when switching organisms. Accordingly, Applicants submit that Mueller does not provide a teaching to suggest hybridizing a probe complementary to the initiation region of the newly synthesized RNA in the assay presently claimed.

Mueller further does not teach or suggest that, contrary to the teaching of Hardy, the assay described in Hardy could be modified to identify initiation inhibitors. Even if one were to decide to attempt the assay of Mueller in a cell-free system derived from a different organism, there is simply no basis for concluding that the use of an RNase protection assay with Hardy's system would be an effective way to identify inhibitors of RNA synthesis <u>initiation</u>. This result was not known until the present invention; the cited references, without the application of hindsight, do not teach or suggest this result or provide the motivation to attempt an assay as presently claimed.

As none of the cited references, alone or in combination, suggest at least these features of claim 31, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to claim 31 and dependent claim 36.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly,

reconsideration and allowance are requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

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